Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial

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SUMMARY

Background: Newer-generation drug-eluting stents that combine ultrathin strut metallic platforms with biodegradable polymers might facilitate vascular healing and improve clinical outcomes in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (PCI) compared with contemporary thin strut second-generation drug-eluting stents. We did a randomised clinical trial to investigate the safety and efficacy of ultrathin strut biodegradable polymer sirolimus-eluting stents versus thin strut durable polymer everolimus-eluting stents in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Methods: The BIOSTEMI trial was an investigator-initiated, multicentre, prospective, single-blind, randomised superiority trial at ten hospitals in Switzerland. Patients aged 18 years or older with acute STEMI who were referred for primary PCI were eligible to participate. Patients were randomly allocated (1:1) to either biodegradable polymer sirolimus-eluting stents or durable polymer everolimus-eluting stents. Central randomisation was done based on a computer-generated allocation sequence with variable block sizes of 2, 4, and 6, which was stratified by centre, diabetes status, and presence or absence of multivessel coronary artery disease, and concealed using a secure web-based system. Patients and treating physicians were aware of group allocations, whereas outcome assessors were masked to the allocated stent. The experimental stent (Orsiro; Biotronik; Bülach, Switzerland) consisted of an ultrathin strut cobalt–chromium metallic stent platform releasing sirolimus from a biodegradable polymer. The control stent (Xience Xpedition/Alpine; Abbott Vascular, Abbott Park, IL, USA) consisted of a thin strut cobalt–chromium stent platform that releases everolimus from a durable polymer. The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial reinfarction (Q-wave and non-Q-wave), and clinically-indicated target lesion revascularisation, within 12 months of the index procedure. All analyses were done with the individual participant as the unit of analysis and according to the intention-to-treat principle. The trial was registered with ClinicalTrials.gov, number NCT02579031.

Findings: Between April 26, 2016, and March 9, 2018, we randomly assigned 1300 patients (1623 lesions) with acute myocardial infarction to treatment with biodegradable polymer sirolimus-eluting stents (649 patients and 816 lesions) or durable polymer everolimus-eluting stents (651 patients and 806 lesions). At 12 months, follow-up data were available for 614 (95%) patients treated with biodegradable polymer sirolimus-eluting stents and 626 (96%) patients treated with durable polymer everolimus-eluting stents. The primary composite endpoint of target lesion failure occurred in 25 (4%) of 649 patients treated with biodegradable polymer sirolimus-eluting stents and 36 (6%) of 651 patients treated with durable polymer everolimus-eluting stents (difference –1·6 percentage points; rate ratio 0·59, 95% Bayesian credibility interval 0·37–0·94; posterior probability of superiority 0·986). Cardiac death, target vessel myocardial reinfarction, clinically-indicated target lesion revascularisation, and definite stent thrombosis were similar between the two treatment groups in the 12 months of follow-up.

Interpretation: In patients with acute STEMI undergoing primary PCI, biodegradable polymer sirolimus-eluting stents were superior to durable polymer everolimus-eluting stents with respect to target lesion failure at 1 year. This difference was driven by reduced ischaemia-driven target lesion revascularisation in patients treated with biodegradable polymer sirolimus-eluting stents compared with durable polymer everolimus-eluting stents.

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INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with acute ST-segment elevation myocardial infarction (STEMI).[1] Newer-generation drug-eluting stents have substantially improved clinical outcomes among patients with acute STEMI compared with bare-metal stents[2] and early-generation durable polymer drug-eluting stents.[3]

Biodegradable polymers and ultrathin stent platforms have been designed to mitigate inflammation and vascular injury, and to promote rapid endothelialisation in patients undergoing PCI. Newer-generation drug-eluting stents that combine cobalt–chromium stent platforms with biodegradable polymers eluting sirolimus were found to be non-inferior[4–6] or superior[7] to contemporary durable polymer everolimus-eluting stents with respect to composite clinical endpoints at 1 year. Subgroup analyses from randomised trials suggested improved clinical outcomes in patients treated with biodegradable polymer drug-eluting stents compared with early-generation[8] and newer-generation durable polymer drug-eluting stents.[9] By contrast, subgroup analyses of patients with acute coronary syndromes enrolled into other randomised non-inferiority trials showed no difference in event numbers between patients treated with biodegradable polymer sirolimus-eluting stents and other newer-generation drug-eluting stents.[5,6,10]

The prothrombotic and inflammatory milieu in patients with acute STEMI[11] poses particular challenges to vascular healing[12] and stent-related clinical outcomes[13] after primary PCI and might reveal the differences among different stent platforms. However, to our knowledge, there are no dedicated randomised controlled trials comparing newer-generation drug-eluting stents in the setting of acute STEMI. Therefore, we did a randomised clinical trial to investigate the safety and efficacy of ultrathin strut biodegradable polymer sirolimus-eluting stents versus thin strut durable polymer everolimus-eluting stents in patients with acute STEMI undergoing primary PCI.

METHODS

Study design and participants

The BIOSTEMI trial was an investigator-initiated, multicentre, prospective, single-blind, randomised superiority trial that compared an ultrathin strut biodegradable polymer sirolimus-eluting stent with a thin strut durable polymer everolimus-eluting stent in patients with acute STEMI undergoing primary PCI at ten hospitals in Switzerland. The study rationale and design have been described previously.[14]

Patients aged 18 years or older with acute STEMI who were referred for primary PCI within 24 h after symptom onset and with at least one culprit coronary lesion in one or more native target coronary vessels suitable for drug-eluting stent implantation were eligible to participate in the trial. Acute STEMI was defined as new persistent ST-segment elevation of 1 mm or greater in two or more contiguous leads, a new (or presumed new) left bundle branch block, or new (or presumed new) horizontal or down-sloping ST-segment depression of 1 mm or greater in leads V_1–V_3. Patients presenting with cardiogenic shock were eligible for inclusion. Patients with acute myocardial infarction due to stent thrombosis or those with mechanical complications were excluded. For full inclusion and exclusion criteria see the appendix (p 2).

All conscious patients who were able to make an informed decision gave written informed consent for participation in the study before randomisation. Oral consent was accepted in conscious patients who were unable to read, interpret, and sign the informed consent form before intervention, but had to be confirmed as soon as possible after the intervention. Unconscious patients could be included with the consent of an independent physician not involved in the study that was called in to safeguard the interests of the patient. Consent by proxy had to be confirmed by the patient as soon as possible. In patients who revoked preliminary consent, data collected up to the time of withdrawal were anonymised and included in the analysis up to the time of revoked consent.

The study protocol complied with the Declaration of Helsinki and was approved by the institutional ethics committees at each participating site. An academic steering committee designed the study.

The Clinical Trials Unit Bern (University of Bern, Switzerland) conducted the study and managed all study data. The trial statisticians did all analyses.

Randomisation and masking

Patients were randomly allocated (1:1) to either biodegradable polymer sirolimus-eluting stents or durable polymer everolimus-eluting stents. After successful crossing of the first target lesion with a coronary guidewire, central randomisation was done based on a computer-generated allocation sequence with variable block sizes of 2, 4, and 6, which was stratified by centre, diabetes status, and presence or absence of multivessel coronary artery disease, and concealed using a secure web-based system. Patients and treating physicians were aware of group allocations, whereas outcome assessors were masked to the allocated stent.

Procedures

The experimental stent (Orsiro; Biotronik; Bülach, Switzerland) consists of an ultrathin strut (60 µm for stent diameters ≤3·0 mm and 80 µm for stent diameters >3·0 mm) cobalt–chromium metallic stent platform covered by an amorphous, hydrogen-rich, silicon-carbide passive layer, and an asymmetric biodegradable poly-Llactic acid polymer active coating that releases sirolimus at a dose of 1·4 µg per mm² stent surface over a period of 12–14 weeks.[15] The control stent (Xience Xpedition/Alpine; Abbott Vascular, Abbott Park, IL, USA) consists of a thin strut (81 µm) cobalt–chromium stent platform that releases everolimus from a durable poly-n-butylmethacrylate and vinylidine fluoride and hexafluoropropylene copolymer.

Primary PCI was done in accordance with current guidelines at the time of enrolment. Intraprocedural medications included unfractionated heparin (5000 IU or 70–100 IU per kg of bodyweight) or bivalirudin. Glycoprotein IIb/IIIa inhibitors were administrated at the discretion of the operator. Dual antiplatelet therapy was started before or at the time of primary PCI and consisted of acetylsalicylic acid (loading dose 250–500 mg, maintenance dose 100 mg per day) in combination with preferably prasugrel (loading dose 60 mg; maintenance dose 10 mg per day) or

ticagrelor (loading dose 180 mg; maintenance dose 90 mg twice per day), or alternatively clopidogrel (loading dose 600 mg, maintenance dose 75 mg per day) for the recommended duration of 12 months. There was no restriction with respect to the type or number of lesions treated. In patients with multivessel disease, revascularisation of all lesions in non-culprit vessels was done with uniform use of the randomly allocated study stent within the same procedure or during subsequent staged procedures, which were permitted within 3 months of the index procedure, at the investigator's discretion.

Clinical follow-up was done at 30 days by telephone interview to assess for adverse events. At 1 year, patients underwent a physicial examination and a 12-lead electrocardiogram in an office visit.

Outcomes

The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial reinfarction (Q-wave and non-Q-wave), and clinically-indicated target lesion revascularisation, within 1 year of the index procedure. Secondary endpoints were all-cause death (cardiac and non-cardiac) at 30 days, 1 year, and 2 years; cardiac death at 30 days, 1 year, and 2 years; myocardial infarction (Q-wave and non-Q-wave) at 30 days, 1 year, and 2 years; clinically-indicated and not clinically-indicated target lesion revascularisation at 30 days, 1 year, and 2 years; clinically-indicated and not clinically-indicated target vessel revascularisation at 30 days, 1 year, and 2 years; target vessel failure as a composite of cardiac death, any myocardial infarction, or any target vessel revascularisation at 30 days, 1 year, and 2 years; definite stent thrombosis and definite or probable stent thrombosis at 30 days, 1 year, and 2 years, and device, lesion, and procedural success. 2-year results are planned to be reported in a future publication. Analyses of all-cause death, cardiac death, target vessel myocardial infarction, definite stent thrombosis, and probable stent thrombosis were also done in the safety population, defined as all participants who received at least one biodegradable polymer sirolimus-eluting stent or one durable polymer everolimus-eluting stent.

Central and onsite data were monitored by the Clinical Trials Unit of the University of Bern. All participating sites received three onsite monitoring visits. Onsite monitors verified informed consent in all participants and checked key data in a random sample of 10% of enrolled patients at each participating site. Data were centrally monitored by the study statistician who checked each variable for entry, validity, consistency, and plausibility on an ongoing basis. An independent clinical events committee masked to treatment assignment adjudicated all study endpoints using standard definitions. The clinical events committee reviewed medical documentation, discharge summaries, and angiogaphy films if needed to assess safety and adverse events.

Statistical analysis

We used Bayesian statistical methods with robust priors incorporating historical data from 407 patients with acute STEMI included in the BIOSCIENCE trial4 to assess the primary endpoint.

We hypothesised that biodegradable polymer sirolimus- eluting stents were superior to durable polymer everolimus-eluting stents with respect to the primary composite endpoint of target lesion failure within 12 months of the index procedure. Based on the results of the acute STEMI subgroup analysis of the BIOSCIENCE trial,[9] we assumed a rate ratio (RR) of the primary endpoint of 0·60, from 7·0% with durable polymer everolimus-eluting stents to 4·2% with biodegradable polymer sirolimus-eluting stents. The study protocol defined superiority of biodegradable polymer sirolimus-eluting stents over durable polymer everolimus-eluting stents if the posterior probability for an RR of less than 1 was greater than 0·975. 1250 patients were needed to show superiority of biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents with 80% or greater power. All analyses were done with the individual participant as the unit of analysis and according to the intention-to-treat principle. Follow-up time was censored at the time of an event, loss to follow-up, or end of the planned follow-up, whichever occurred first.

We used Bayesian log Poisson models incorporating historical data from the BIOSCIENCE trial.[4] We estimated the log incidence rates in each of the two study groups for all clinical endpoints from the BIOSCIENCE trial (407 patients) with Bayesian log Poisson models with minimally informative priors

(μ=0, τ=0·111) and an offset term (log of the time at risk). Then, we used the posterior mean and SD of the log incidence rates in BIOSCIENCE as informative priors for the analysis of BIOSTEMI endpoints. For each endpoint, the robust prior was a 50:50 mixture between the historical informative prior (μ=posterior mean [BIOSCIENCE], τ=posterior SD [BIOSCIENCE]) and a vague prior (μ=0, τ=0·111) based on Bernoulli distributions. By use of Bayesian log Poisson models with time at risk fitted as an offset, we estimated the incidence in both study groups for all endpoints. The use of robust priors efficiently controlled the type I error rate by downweighting the contribution of historical information from the BIOSCIENCE trial if it turned out to be inconsistent with the information collected in the BIOSTEMI trial. RRs were reported as the median of the Bayesian posterior distribution and associated 95% Bayesian credibility intervals (CrIs) were reported as the 2·5th and 97·5th percentiles of the Bayesian posterior distribution. Within the framework of this analysis, CrIs were interpreted similarly to CIs.[16]

We did prespecified subgroup analyses according to diabetes and multivessel disease at baseline and post-hoc subgroup analyses according to age, sex, body-mass index, vessel diameter, lesion length, and renal failure. All subgroup analyses were done with the same approach as the main analyses. Specifically, robust historical priors were constructed by analysis of the primary endpoint in each subgroup of patients in the BIOSCIENCE trial with acute STEMI. These subgroup-specific robust historical priors were used to analyse the data from patients in the BIOSTEMI trial. For descriptive purposes, we derived Kaplan-Meier curves for patients included in the acute STEMI subgroup of the BIOSCIENCE trial and in the BIOSTEMI trial separately and combined. Full details including model equations and graphical representations of the priors are provided in the statistical analysis plan (appendix pp 94–121).

Statistical analyses were done using R Studio version 3.5.2 and STATA version 15. The trial was registered with ClinicalTrials.gov, number NCT02579031.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DH, SW, JFI, OM, PJ, and TP had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between April 26, 2016, and March 9, 2018, we randomly assigned 1300 patients with acute STEMI and 1623 culprit lesions to treatment with biodegradable polymer sirolimus-eluting stents (649 patients and 816 lesions) or durable polymer everolimus-eluting stents (651 patients and 806 lesions; figure 1). At 1 year, follow-up data were available for 614 (95%) patients treated with biodegradable polymer sirolimus-eluting stents and 626 (96%) patients treated with durable polymer everolimus-eluting stents (figure 1).

We summarised baseline clinical, angiographic, and procedural characteristics (tables 1, 2). 73 (11%) of 649 patients treated with biodegradable polymer sirolimus-eluting stents and 82 (13%) of 651 patients treated with durable polymer everolimus-eluting stents presented with diabetes mellitus (table 1). Adherence to and type and duration of antiplatelet therapy were similar in the two treatment groups at 1 year (appendix pp 3–4). At 1 year, 175 (48%) staged procedures were done in the biodegradable polymer sirolimus-eluting stent group and 191 (52%) were done in the durable-polymer everolimus-eluting stent group.

At 1 year of follow-up, the primary composite endpoint of target lesion failure occurred in 25 (4%) patients treated with biodegradable polymer sirolimus-eluting stents and in 36 (6%) patients treated with durable polymer everolimus-eluting stents (table 3). The prespecified criterion for superiority of ultrathin strut biodegradable polymer sirolimus-eluting stents compared with thin strut durable polymer everolimus-eluting stents was met (difference –1·6 percentage points; RR 0·59, 95% Bayesian CrI 0·37–0·94; posterior probability of superiority 0·986; figure 2). We observed little evidence for differences in cardiac death (18 [3%] vs 19 [3%]; difference –0·1 percentage points; RR 0·77, 95% Bayesian CrI 0·43–1·40; posterior probability of superiority 0·806) and target vessel

myocardial reinfarction (5 [1%] vs 6 [1%]; difference –0·1 percentage points; 0·55, 0·19–1·60; posterior probability of superiority 0·875) between treatment groups. Clinically-indicated target lesion revascularisations were more frequent in the durable polymer everolimus-eluting stent group compared with the biodegradable polymer sirolimus-eluting stent group, but this difference was not significant (9 [1%] vs 17 [3%]; difference 1·2 percentage points; 0·55, 0·26–1·13; posterior probability of superiority 0·94; table 3; figure 3; appendix pp 8–9). We observed possible interactions for body-mass index and renal failure for the primary endpoint, with posterior probabilities close to 0·975 (figure 4).

At 1 year, all-cause death occurred in 24 (4%) of 429 patients treated with biodegradable polymer sirolimus-eluting stents and in 22 (3%) of 651 patients treated with durable polymer everolimus-eluting stents (table 3). Myocardial reinfarction occurred in 15 (2%) patients in the biodegradable polymer sirolimus-eluting stent group and in ten (2%) patients in the durable polymer everolimus-eluting stent group, and target lesion revascularisation occurred in 11 (2%) patients treated with biodegradable polymer sirolimus-eluting stents and in 19 (3%) patients treated with durable polymer everolimus-eluting stents (table 3).

At 12 months, definite stent thrombosis was documented in six (1%) patients treated with biodegradable polymer sirolimus-eluting stents and in eight (1%) patients treated with durable polymer everolimus-eluting stents (difference –0·3 percentage points; RR 0·68, 95% Bayesian CrI 0·22–1·89; posterior probability of superiority 0·762; table 3).

Clinical outcomes and Bayesian posterior probabilities with and without inclusion of historical information from the cohort of patients with acute STEMI in the BIOSCIENCE trial in the robust prior are provided in the appendix (pp 5–6). The RR of the primary endpoint of target lesion failure was 0·69 (95% Bayesian CrI 0·41–1·15), with a posterior probability of superiority of 0·923, which increased to 0·986 after incorporation of historical information.

In our analyses of the safety population, results for all-cause death, cardiac death, target-vessel myocardial infarction, definite stent thrombosis, and probable stent thrombosis were consistent with our primary analyses (appendix p 7).

DISCUSSION

In this multicentre, randomised trial with a Bayesian design, we found that ultrathin strut biodegradable polymer sirolimus-eluting stents were superior to thin strut durable polymer everolimus-eluting stents with respect to the incidence of target lesion failure at 1 year of follow-up among patients with acute STEMI undergoing primary PCI. To our knowledge, the present study represents the first direct comparison between two newer-generation drug-eluting stents in patients with acute STEMI.

Early-generation[17,18] and newer-generation drug-eluting stents[2] have progressively improved safety and efficacy outcomes compared with bare-metal stents in patients with acute STEMI undergoing primary PCI. Newer-generation drug-eluting stents that combine thin strut stent platforms with biocompatible durable polymer coatings were associated with further reductions in the risk of repeat revascularisation and stent thrombosis after primary PCI compared with early-generation thicker strut durable polymer drug-eluting stents.[18] Newer-generation drug-eluting stents that combine thinner stent platforms with biodegradable or biocompatible polymer coatings have been introduced with the intent to further reduce thrombogenicity and vascular injury, accelerate endothelialisation, and potentially improve clinical outcomes.[11]

In the present study, the difference in the primary endpoint between the two study groups was largely driven by fewer cases of clinically-indicated target lesion revascularisation in patients treated with biodegradable polymer sirolimus-eluting stents compared with durable polymer everolimus-eluting stents. In the BIOFLOW-V trial,19 patients treated with biodegradable sirolimus-eluting stents were found to have fewer cases of ischaemia-driven target lesion revascularisation compared with patients treated with durable polymer everolimus-eluting stents at 2 years of follow-up. In the BIORESORT trial,[5] which included 3514 patients, of whom almost a third presented with STEMI, the primary endpoint of target lesion failure was similar between patients treated with biodegradable polymer sirolimus-eluting stents, biodegradable polymer everolimus-eluting stents, and durable polymer zotarolimus-eluting stents at 1 year. Between 1 year and 2 years, target lesion revascularisations were significantly reduced in patients treated with biodegradable polymer

sirolimus-eluting stents compared with patients treated with durable polymer zotarolimus-eluting stents.20 Additionally, in patients with small vessel disease, target lesion revascularisation at 3 years was significantly lower in patients treated with biodegradable polymer sirolimus-eluting stents compared with biodegradable polymer everolimus-eluting stents and durable polymer zotarolimus-eluting stents.21 In the BIONYX trial,6 durable polymer zotarolimus-eluting stents were non-inferior to biodegradable polymer sirolimus-eluting stents with no interaction regarding presentation with an acute coronary syndrome or stable coronary artery disease.

The difference in the primary endpoint in our study was driven by clinically-indicated target lesion revascularisation. By contrast, the lower incidence of target lesion failure at 12-month follow-up reported in the BIOFLOW-V trial7 was driven by significantly fewer cases of target vessel myocardial infarction in patients treated with ultrathin strut biodegradable polymer sirolimus-eluting stents compared with thin strut durable polymer everolimus-eluting stents. The absence of a robust difference in the incidence of target vessel myocardial reinfarction between the two treatment groups in our study might be explained by the difficulty in detection of periprocedural myocardial reinfarction in the setting of acute STEMI.[22]

The degradation time of the poly-L-lactic acid polymer used in the ultrathin strut sirolimus-eluting stent extends well beyond a year and might affect very late clinical outcomes. Additionally, the metallic stent platform composition, geometry, and strut thickness could affect clinical outcomes in patients with acute STEMI undergoing primary PCI. Ultrathin strut drug-eluting stents have been associated with a lower risk of target lesion failure and myocardial infarction compared with thin strut drug-eluting stents in a meta-analysis of randomised trials.[23] A reduction in strut thickness has been shown to mitigate inflammation, vessel injury, neointimal proliferation, and thrombus formation.[11,24,25] These findings are particularly relevant in the inflammatory milieu of acute STEMI and might explain the differences we observed in the incidence of target lesion failure and target lesion revascularisation in patients treated with biodegradable polymer sirolimus-eluting stents compared with those treated with durable polymer everolimus-eluting stents. The clinical benefit of biodegradable polymer sirolimus-eluting stents emerged within the first 12 months after drug-

eluting stent implantation, well before complete degradation of the poly-L-lactic acid polymer and exposure to the passive silicon carbide coating previously shown to reduce thrombogenicity and facilitate endothelialisation.[15] Minimisation of strut thickness might be an alternative strategy to completely biodegradable scaffolds, which have fallen short of expectations in randomised trials.[26] The pathophysiological correlate for a reduction in clinical events within the first year after stent implantation in patients treated with biodegradable polymer sirolimus-eluting stents compared with durable polymer everolimus-eluting stents warrants further study. Intravascular imaging studies and histopathological analysis might be needed to elucidate differences in the pattern of vascular inflammation and stent strut endothelialisation.

In our analysis of the BIOSTEMI trial, we employed Bayesian methods to incorporate the results from the subgroup of patients with acute STEMI in the BIOSCIENCE trial (407 patients with acute STEMI representing 19% of the full BIOSCIENCE trial cohort) as prior information. This approach was prespecified and informed the power calculation of the BIOSTEMI trial, therefore allowing for increased efficiency by reducing the number of participants and trial duration. Compared with conventional meta-analyses, in which results from BIOSCIENCE and BIOSTEMI would be pooled using a fixed-effect meta-analysis, the use of robust priors in this approach efficiently controlled the type I error rate by downweighting the contribution of the historical information from the BIOSCIENCE trial if the historical information turned out to be inconsistent with the information collected in the BIOSTEMI trial. Accordingly, this approach strengthens the validity of our results.

The results of the present study should be interpreted in view of several limitations. First, the trial was powered for superiority on the primary composite endpoint of target lesion failure using Bayesian methods and potential differences in individual clinical endpoints should be interpreted cautiously and are therefore hypothesis-generating. Likewise, the trial was not powered to examine differences in the individual endpoints contributing to the composite primary outcome. Nonetheless, treatment effects between this trial and the BIOSCIENCE subgroup with acute STEMI used as historical information in the robust prior were consistent, corroborating the robustness of our findings. Second, follow-up information was missing for 35 (5%) of 649 patients in the

biodegradable polymer sirolimus-eluting stent group and 25 (4%) of 651 patients in the durable polymer everolimus-eluting stent group because of refusal or loss to follow-up at 1 year. Our completeness of follow-up at 1 year was lower than in previous randomised trials of acute STEMI.[27,28] Our study design allowed for provisional inclusion of patients on the basis of oral consent and for provisional inclusion of unconscious patients by consent by proxy. Although this approach might have facilitated the enrolment of an unselected patient population presenting with STEMI, it increased the number of patients who refused follow-up early after randomisation. Additionally, inclusion of patients with cardiogenic shock with high periprocedural risk might have diluted the expected difference between the two treatment groups. Third, beyond stent strut thickness and polymer characteristics, the study stents differ from each other in stent platform geometry, presence of a passive coating, the antiproliferative drug, drug load, and release kinetics. Therefore, the relative contribution of each individual stent component to the improved clinical outcomes observed among patients treated with ultrathin strut biodegradable polymer sirolimus-eluting stents compared with those treated with thin strut durable polymer everolimus-eluting stents cannot be definitively understood. Fourth, patients and treating physicians were not masked to treatment allocation. Fifth, we did not undertake post-procedural quantitative coronary angiography of the target lesion, nor was it mandatory to control the stent result using intracoronary imaging. Sixth, the clinical event committee relied on the information on clinical symptoms documented in the patient chart, which might have been biased by the judgment of the operator. Finally, the study was limited to one year of follow-up. Extended follow-up of previous trials in the setting of acute STEMI showed that the clinical benefits of newer-generation drug-eluting stents were maintained during long-term follow-up.29,30 The long-term effects of ultrathin strut biodegradable polymer sirolimus-eluting stents compared with thin strut durable polymer everolimus-eluting stents among patients with acute STEMI after degradation of the poly-L-lactic acid polymer therefore need evaluation during extended follow-up.

In patients with acute STEMI undergoing primary PCI, ultrathin strut biodegradable polymer sirolimuseluting stents were superior to thin strut durable polymer everolimus-eluting stents with

respect to the primary endpoint of target lesion failure at 1 year. This difference was driven by fewer ischaemia-driven target lesion revascularisations in patients treated with biodegradable polymer sirolimus-eluting stents compared with patients treated with durable polymer everolimus-eluting stents.

BOX: RESEARCH IN CONTEXT

Evidence before this study

In patients undergoing primary percutaneous coronary intervention (PCI) for acute myocardial infarction, randomised clinical trials have shown lower rates of the composite outcome of all-cause death, myocardial infarction, or revascularisation in patients treated with newer-generation drug-eluting stents compared with bare-metal stents. We searched PubMed from inception up to June 30, 2019, with no language restrictions, with the search terms “drug-eluting stent and acute myocardial infarction” and “drug-eluting stent and ST-segment elevation myocardial infarction”, and found no randomised head-to-head trials assessing the incremental benefit of different drug-eluting stents in patients with acute myocardial infarction. The available evidence shows favourable patient-oriented clinical outcomes in patients with myocardial infarction treated with newer-generation drug-eluting stents compared with bare-metal stents.

Added value of this study

To our knowledge, the BIOSTEMI trial is the first randomised comparison of two newer-generation drug-eluting stents in patients undergoing primary PCI for reperfusion therapy of acute myocardial infarction. The results of the present study showed fewer target lesion failures in patients treated with biodegradable polymer sirolimus-eluting stents compared with durable polymer everolimus-eluting stents after 1 year of follow-up.

Implications of all the available evidence

Although newer-generation drug-eluting stents are superior to bare-metal stents in patients undergoing primary PCI for acute myocardial infarction, refinements in stent technology combining ultrathin stent platforms with biodegradable polymers could further improve clinical outcomes.

CONTRIBUTORS

JFI, OM, EE, DH, PJ, SW, and TP conceived the study. JFI, OM, DH, PJ, SW, and TP designed the study. JFI, OM, MR, DJK, IM, DW, CK, MT, SS, EE, MV, SW, and TP acquired the data. SL and DH analysed the data and interpreted the results in collaboration with JFI, OM, MZ, PJ, SW, TP, and all other authors. JFI and TP wrote the first draft of the report. All authors critically revised the report for important intellectual content and approved the final version.

DECLARATION OF INTERESTS

JFI reports a research grant and personal fees from Biotronik during the conduct of the study; and grants and personal fees from Biotronik, Philips Volcano, and AstraZeneca, and personal fees from Terumo, Medtronic, and Cardinal Health, outside the submitted work. DH is affiliated with Clinical Trials Unit Bern (CTU Bern), University of Bern (Bern, Switzerland), which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations. In particular, pharmacetical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. MR reports institutional research grants from Terumo, Boston Scientific, Medtronic, Abbott Vascular, and Biotronik, outside the submitted work. DJK reports grants from the University Clinic for Cardiology, Inselspital Bern, Swizerland, during the conduct of the study. SS reports grants from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott and personal fees from Boston Scientific, BTG, and Teleflex, outside the submitted work. EE reports grants from Biotronik during the conduct of the study. MV reports grants

and personal fees from Abbott, Terumo, and AstraZeneca, personal fees from Bayer, Dalichi Sankyo, Amgen, Alvimedica, Idorsia, Coreflow, Vifor, Bristol-Myers Squibb, and iVascular, and grants from Medicure, ouside the submitted work. PJ serves as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St Jude Medical, and The Medicines Company, and received research grants to their institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company, and honoraria to their institution for participation in advisory boards from Amgen, but has not received personal payments by any pharmaceutical company or device manufacturer. PJ is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases. This research was completed, in part, with funding from the Canada Research Chairs Programme. SW received research grants to their institution from Amgen, Abbott, Bayer, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Edwards Lifesciences, Medtronic, Polares, and Sinomed, outside the submitted work, and research grants from Biotronik during the conduct of the study. TP received research grants to their institution and speaker fees from Biotronik, during the conduct of this study, research grants to their institution from Boston Scientific and Edwards Lifesciences, and speaker fees from Boston Scientific, outside the submitted work, and serves as a consultant for HighLife SAS. All other authors declare no competing interests.

DATA SHARING

The BIOSTEMI trial is an investigator-initiated trial. Multiple substudies were predefined. Internal investigators who actively participated in the study and who provide a methodologically sound study proposal will be granted priority access to the study data for a period of 24 months. The study protocol underlying this paper will immediately be available with the published Article (appendix pp 10–93). After 24 months, data underlying this manuscript plus relevant documentation will be made available to external investigators not affiliated to the trial whose proposed use of the data has been approved by an independent review committee identified by the steering committee for this purpose. Data will be deposited at https://boris.unibe.ch/132665/ where study proposals can also be filed.

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REFERENCES

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119–77.
2. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2019; 393: 2503–10.
3. de Waha A, King LA, Stefanini GG, et al. Long-term outcomes of biodegradable versus durable polymer drug-eluting stents in patients with acute ST-segment elevation myocardial infarction: a pooled analysis of individual patient data from three randomised trials. EuroIntervention 2015; 10: 1425–31.
4. Pilgrim T, Heg D, Roffi M, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. Lancet 2014; 384: 2111–22.
5. von Birgelen C, Kok MM, van der Heijden LC, et al. Very thin strut biodegradable polymer everolimus-eluting and sirolimus-eluting stents versus durable polymer zotarolimus-eluting stents in allcomers with coronary artery disease (BIO-RESORT): a three-arm, randomised, non-inferiority trial. Lancet 2016; 388: 2607–17.
6. von Birgelen C, Zocca P, Buiten RA, et al. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt–chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in allcomers with coronary artery disease (BIONYX): an international, single-blind, randomised non-inferiority trial. Lancet 2018; 392: 1235–45.
7. Kandzari DE, Mauri L, Koolen JJ, et al. Ultrathin, bioresorbable polymer sirolimus-eluting stents versus thin, durable polymer everolimus-eluting stents in patients undergoing coronary revascularisation (BIOFLOW V): a randomised trial. Lancet 2017;390: 1843–52.
8. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008; 372: 1163–73.
9. Pilgrim T, Piccolo R, Heg D, et al. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for primary percutaneous coronary revascularisation of acute myocardial infarction. EuroIntervention 2016; 12: e1343–54.
10. Jensen LO, Thayssen P, Maeng M, et al. Randomised comparison of a biodegradable polymer ultrathin strut sirolimus-eluting stent with a biodegradable polymer biolimus-eluting stent in patients treated with percutaneous coronary intervention: the SORT OUT VII trial. Circ Cardiovasc Interv 2016; 9: e003610.
11. Kolandaivelu K, Swaminathan R, Gibson WJ, et al. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. Circulation 2011; 123: 1400–09.
12. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008; 118: 1138–45.
13. Sarno G, Lagerqvist B, Nilsson J, et al. Stent thrombosis in new-generation drug-eluting stents in patients with STEMI undergoing primary PCI: a report from SCAAR. J Am Coll Cardiol 2014; 64: 16–24.

14. Iglesias JF, Muller O, Zaugg S, et al. A comparison of an ultrathin-strut biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent for patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: rationale and design of the BIOSTEMI trial. EuroIntervention 2018; 14: 692–99.
15. Iglesias JF, Roffi M, Degrauwe S, et al. Orsiro cobalt–chromium sirolimus-eluting stent: present and future perspectives. Expert Rev Med Devices 2017; 14: 773–88.
16. Willink R, Lira I. A united interpretation of different uncertainty intervals. Measurement 2005; 38: 61–66.
17. Kalesan B, Pilgrim T, Heinimann K, et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012; 33: 977–87.
18. Bangalore S, Amoroso N, Fusaro M, Kumar S, Feit F. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circ Cardiovasc Interv 2013;6: 378–90.
19. Kandzari DE, Koolen JJ, Doros G, et al. Ultrathin bioresorbable polymer sirolimus-eluting stents versus thin durable polymer everolimus-eluting stents. J Am Coll Cardiol 2018; 72: 3287–97.
20. Kok MM, Zocca P, Buiten RA, et al. Two-year clinical outcome of all-comers treated with three highly dissimilar contemporary coronary drug-eluting stents in the randomised BIO-RESORT trial. EuroIntervention 2018; 14: 915–23.
21. Buiten RA, Ploumen EH, Zocca P, et al. Outcomes in patients treated with thin-strut, very thin-strut, or ultrathin-strut drug-eluting stents in small coronary vessels: a prespecified analysis of the randomized BIO-RESORT trial. JAMA Cardiol 2019; published online May 21. DOI:10.1001/jamacardio.2019.1776.
22. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010; 5: 871–74.
23. Bangalore S, Toklu B, Patel N, Feit F, Stone GW. Newer-generation ultrathin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease. Circulation 2018; 138: 2216–26.
24. Kastrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001; 103: 2816–21.
25. Pache J, Kastrati A, Mehilli J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. J Am Coll Cardiol 2003; 41: 1283–88.
26. Ali ZA, Serruys PW, Kimura T, et al. 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. Lancet 2017; 390: 760–72.
27. Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 2012; 380: 1482–90.
28. Räber L, Kelbæk H, Ostojic M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA 2012; 308: 777–87.
29. Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. Lancet 2016; 387: 357–66.

30. Räber L, Yamaji K, Kelbæk H, et al. Five-year clinical outcomes and intracoronary imaging findings of the COMFORTABLE AMI trial: randomized comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction. Eur Heart J 2019; 40: 1909–19.

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582 **TABLES**

583 **Table 1:** Baseline clinical characteristics

	Biodegradable polymer sirolimus-eluting stent (n=649)	Durable polymer everolimus-eluting stent (n=651)
Age (years)	62·2 (11·8)	63·2 (11·8)
Sex		
Female	136 (21%)	174 (27%)
Male	513 (79%)	477 (73%)
Body-mass index (kg/m²)	26·9 (4·3)	26·8 (4·3)
Diabetes mellitus	73 (11%)	82 (13%)
Oral treatment	43 (7%)	60 (9%)
Insulin dependent	22 (3%)	15 (2%)
Hypertension	281 (43%)	297 (46%)
Hypercholesterolaemia	304 (47%)	302/644 (47%)
Active smoker	294 (45%)	250/635 (39%)
Previous myocardial infarction	27 (4%)	24 (4%)
Previous percutaneous coronary intervention	29 (4%)	34 (5%)
Previous coronary artery bypass surgery	2 (<1%)	8 (1%)
Previous stroke	16 (2%)	19 (3%)
Peripheral arterial disease	16 (2%)	17 (3%)
Chronic renal failure (estimated glomerular filtration rate <60 mL/min)	76/633 (12%)	78/632 (12%)
Left ventricular ejection fraction	49·0 (11·0)*	48·4 (11·2)†
Baseline medication		
Aspirin	77/614 (13%)	83/614 (14%)
Clopidogrel	6/614 (1%)	5/615 (1%)
Prasugrel	1/614 (<1%)	1/615 (<1%)
Ticagrelor	6/614 (1%)	3/615 (<1%)
Any dual antiplatelet therapy	10/614 (2%)	5/614 (1%)
Oral anticoagulant	8/611 (1%)	10/616 (2%)
Novel oral anticoagulants	10/611 (2%)	7/616 (1%)
Any anticoagulant treatment	18/611 (3%)	17/617 (3%)
Statin	87/610 (14%)	87/610 (14%)
Angiotensin-converting enzyme inhibitor	52/607 (9%)	62/614 (10%)
β blocker	89/607 (15%)	82/609 (13%)

Data are n (%), mean (SD), or n/N (%). *n=394. †n=407.

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Table 2: Baseline angiographic and procedural characteristics

	Biodegradable polymer sirolimus-eluting stent	Durable polymer everolimus-eluting stent	p value
Number of patients	649	651	..
Number of lesions	816	806	..
Target vessel location per lesion	..	..	0·133
Left main coronary artery	10 (1%)	9 (1%)	..
Left anterior descending artery	316 (39%)	357 (44%)	..
Left circumflex artery	143 (18%)	137 (17%)	..
Right coronary artery	346 (42%)	302 (37%)	..
Saphenous vein graft	1 (<1%)	1 (<1%)	0·993
Number of lesions per patient*	1·26 (0·57)	1·24 (0·52)	0·756
Number of lesions per patient†	..	..	0·756
0	1 (<1%)	0	..
1	516 (80%)	523 (80%)	..
2	103 (16%)	103 (16%)	..
3	23 (4%)	23 (4%)	..
≥4	6 (1%)	2 (<1%)	..
Type of intervention	..	..	0·302
PCI	797 (98%)	793 (98%)	..
Plain balloon angioplasty	17 (2%)	13 (2%)	..
Coronary artery bypass graft	1 (<1%)	0	..
Failed PCI	1 (<1%)	0	..
Baseline thrombolysis in myocardial infarction flow	..	..	0·206
0 or 1	448 (55%)	473 (59%)	..
2	108 (13%)	115 (14%)	..
3	257 (31%)	215 (27%)	..
Post-primary PCI thrombolysis in myocardial infarction flow	..	..	0·355
0 or 1	5 (1%)	3 (<1%)	..
2	17 (2%)	25 (3%)	..
3	791 (97%)	778 (97%)	..
Restenotic lesion	11 (1%)	13 (2%)	0·740
Total occlusion	400 (49%)	443 (55%)	0·024
Chronic total occlusion	1 (<1%)	3 (<1%)	0·335
Thrombus aspiration	243 (30%)	250 (31%)	0·675
Total number of stents implanted	1·37 (0·64)‡	1·39 (0·66)§	0·789
Total stent length (mm)	31·91 (18·21)‡	33·92 (19·76)§	0·051
Maximum stent diameter (mm)	3·17 (0·52)‡	3·16 (0·50)§	0·705

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	Biodegradable polymer sirolimus-eluting stent	Durable polymer everolimus-eluting stent	p value
(Continued fom previous page)			
Maximum pressure (atm)	13·49 (3·24)¶	13·82 (3·23)¶	0·027
Overlapping stents	219/797 (27%)	236/793 (30%)§	0·407
Pre-dilatation	215/797 (27%)	202/793 (25%)	0·549
Post-dilatation	525/797 (66%)	528/793 (67%)	0·738
Long lesion (total stent length >20 mm)	567/797 (71%)	563/793 (71%)	0·814
Small vessel (minimum stent diameter <3 mm)	292 (36%)	321 (40%)	0·125
Bifurcation treatment (including left main coronary artery)	101 (12%)	115 (14%)	0·400
Type of stent per lesion	..	..	0·549
Biodegradable polymer sirolimus-eluting stent	791/797 (99%)	2/793 (<1%)§	..
Durable polymer everolimus-eluting stent	1/797 (<1%)	789/793 (99%)	..
Other drug-eluting stent	5/797 (1%)	3/793 (<1%)	..
Bare metal stent	1/797 (<1%)	0	..
Intra-aortic balloon pump	3/649 (<1%)	5/651 (1%)	0·486
Vasopressors	14/649 (2%)	12/651 (2%)	0·686
Cardiogenic shock	20/649 (3%)	21/651 (3%)	0·876

Data are n, n (%),mean (SD), or n/N (%). Unless otherwise indicated, p values are from mixed models for the per-lesion analyses, accounting for lesions nested within patients (general linear mixed models for continuous variables and generalised linear mixed models for counts). PCI=percutaneous coronary intervention. *p values from Poisson regression for per patient analyses. †p values from χ^2 test for per-patient analyses. ‡n=797. §n=793. ¶n=789.

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589 **Table 3:** Clinical outcomes at 1 year

	Biodegradable polymer sirolimus-eluting stent (n=649)	Durable polymer everolimus-eluting stent (n=651)	RR (95% Bayesian CrI)	Bayesian posterior probability
Target lesion failure (primary endpoint)	25 (4%)	36 (6%)	0·59 (0·37–0·94)	0·986
Cardiac death	18 (3%)	19 (3%)	0·77 (0·43–1·40)	0·806
All-cause death	24 (4%)	22 (3%)	0·97 (0·58–1·62)	0·553
Target vessel myocardial reinfarction	5 (1%)	6 (1%)	0·55 (0·19–1·60)	0·875
Target vessel myocardial reinfarction (Q-wave)	2 (<1%)	2 (<1%)	0·42 (0·07–2·41)	0·850
Target vessel myocardial reinfarction (non-Q-wave)	3 (<1%)	4 (1%)	0·66 (0·19–2·18)	0·750
Myocardial reinfarction (any)	15 (2%)	10 (2%)	1·21 (0·60–2·46)	0·294
Myocardial reinfarction (Q-wave)	3 (<1%)	2 (<1%)	0·63 (0·13–3·52)	0·726
Myocardial reinfarction (non-Q-wave)	12 (2%)	8 (1%)	1·50 (0·66–3·44)	0·165
Any repeat revascularisation	23 (4%)	31 (5%)	0·81 (0·50–1·28)	0·817
Any target lesion revascularisation	11 (2%)	19 (3%)	0·57 (0·28–1·12)	0·949
Clinically-indicated target lesion revascularisation	9 (1%)	17 (3%)	0·55 (0·26–1·13)	0·949
Any target vessel revascularisation	13 (2%)	25 (4%)	0·59 (0·33–1·05)	0·964
Clinically-indicated target vessel revascularisation	11 (2%)	23 (4%)	0·58 (0·31–1·07)	0·959
Target vessel failure	29 (4%)	44 (8%)	0·61 (0·41–0·92)	0·991
Death, myocardial infarction, or any repeat revascularisation	49 (8%)	53 (8%)	0·90 (0·64–1·26)	0·737
Definite stent thrombosis	6 (1%)	8 (1%)	0·68 (0·22–1·89)	0·762
Probable stent thrombosis	5 (1%)	3 (<1%)	1·75 (0·48–7·26)	0·201
Definite or probable stent thrombosis	10 (2%)	11 (2%)	0·69 (0·32–1·69)	0·803
Bleeding Academic Research Consortium bleeding type 3–5	22 (3%)	15 (2%)	1·26 (0·73–2·45)	0·205

Data are n (%) as observed in the BIOSTEMI trial. RRs and CrIs are estimated from Bayesian log Poisson models with robust priors incorporating data from the STEMI subgroup of the BIOSCIENCE trial (number of iterations: burn-in 50 000; posterior 50 000; mixing weight 0·50 based on Bernoulli distributions; SD of vague prior distribution 3). Bayesian posterior probability corresponds to Bayesian posterior probability for RR <1·0. RR=rate ratio. CrI=credibility interval.

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592 **FIGURES**

593 **Figure 1:**

594 Trial profile

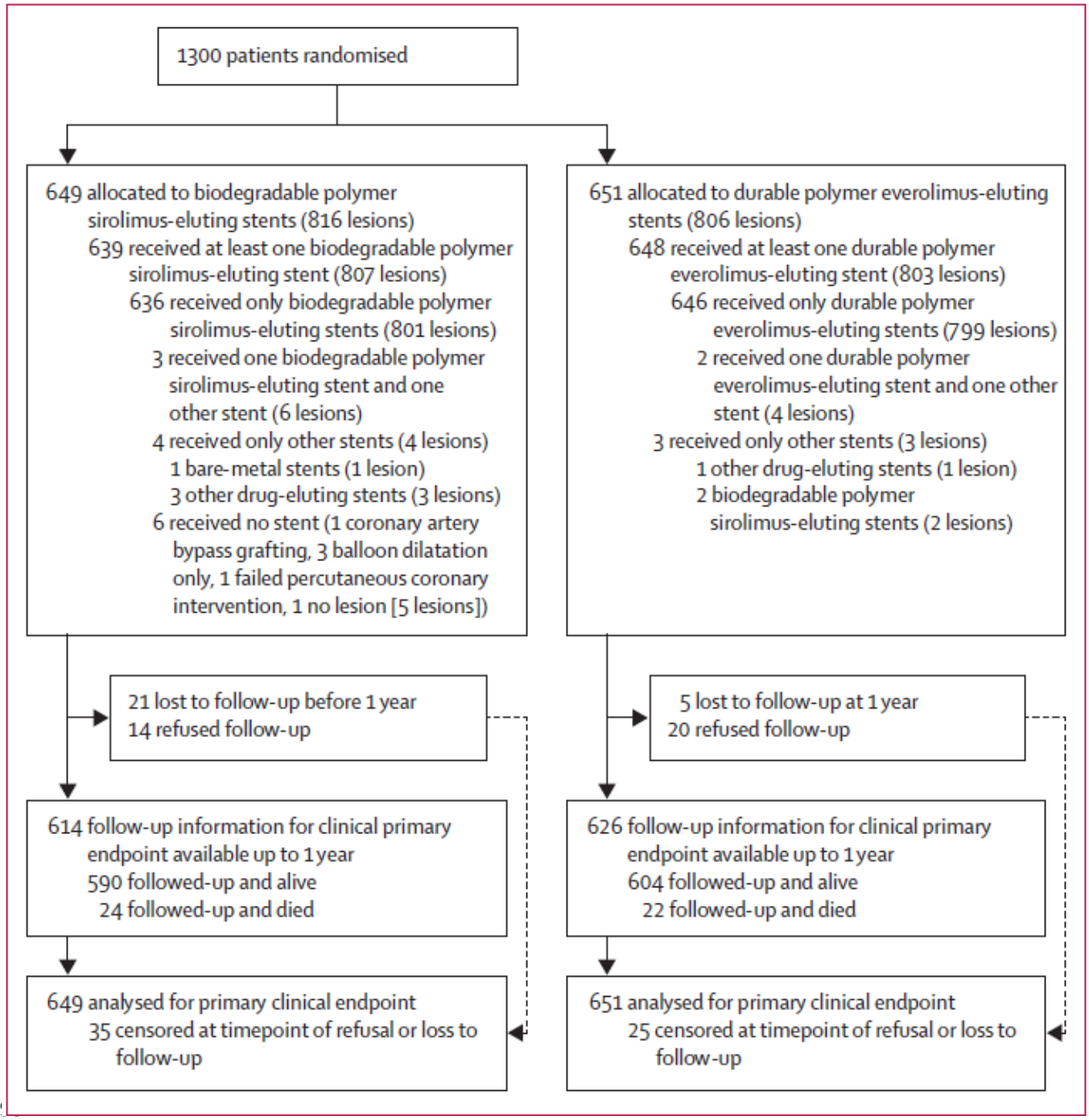

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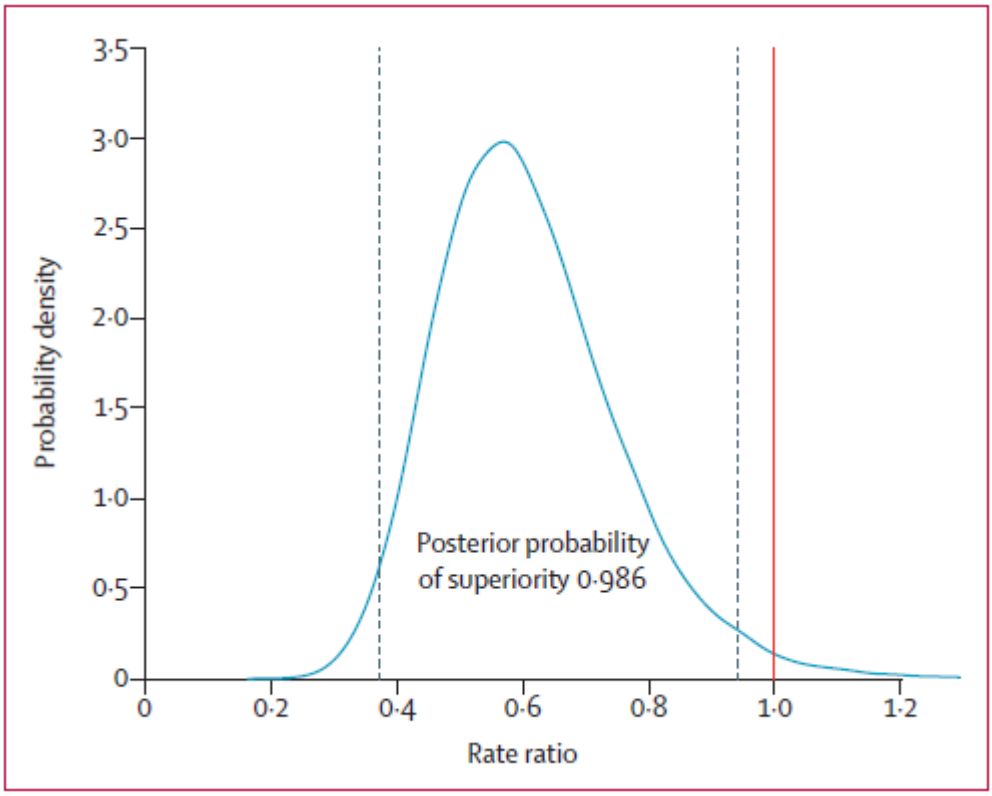
Figure 2:

Posterior distribution of the RR of the primary endpoint.

Posterior distribution of the RR derived from Bayesian log Poisson models with robust priors incorporating data from the STEMI subgroup of the BIOSCIENCE trial. The solid red vertical line indicates the superiority margin. Dashed vertical lines indicate the lower and upper limits of the 95% Bayesian credibility interval. RR=rate ratio.



606 **Figure 3:**

607 Time-to-event curves for target lesion failure (A), cardiac death (B), target vessel myocardial

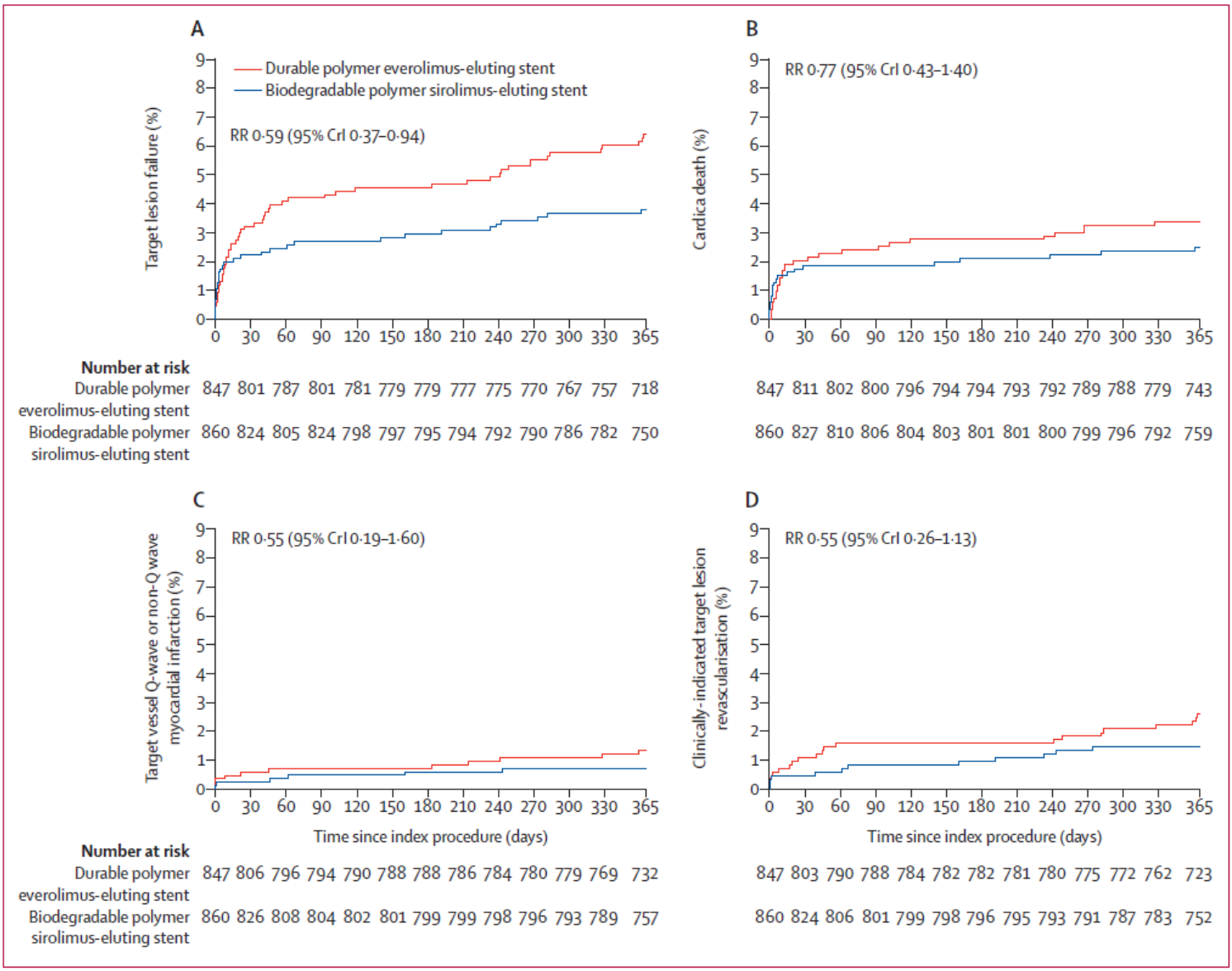
608 infarction (C), and clinically indicated target lesion revascularisation (D) in patients with ST-segment

609 elevation myocardial infarction.

610 RRs and CrIs estimated from Bayesian log Poisson models with robust priors incorporating data from

611 the STEMI subgroup of the BIOSCIENCE trial. RR=rate ratio. CrI=Bayesian credibility interval.

612



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615 **Figure 4:**

616 Clinical outcomes at 1 year according to subgroups

617 Bayesian posterior probability is the Bayesian posterior probability of RR<1·0 within each subgroup.

618 The Bayesian posterior probability of the interaction is the Bayesian posterior probability of a

619 difference between the two subgroups. RR=rate ratio. *Renal failure was defined as creatinine-

620 estimated glomerular filtration rate of less than 60 mL/min using the modification of diet in renal

621 disease formula. †Small vessels were defined as stent diameter in any lesion ≤3·0 mm. ‡Long lesions

622 were defined as total stent length in any lesion ≥20 mm.

623